REMARKS

Claims 48-57 and 60-62 were rejected and remain pending. In light of the following remarks, Applicants respectfully request reconsideration and allowance of claims 48-57 and 60-62.

Telephonic Interview

Applicants' agent thanks the Examiner for the courtesy of the telephonic interview on March 3, 2004. The substance of the telephonic interview involved the 35 U.S.C. §§ 112 and 103 rejections and arguments presented herein.

Withdrawn rejections

Applicants acknowledge the withdrawal of the objection to claim 61. Applicants also acknowledge the withdrawal of the rejection of claims 48-57 and 60-62 under 35 U.S.C. § 112, second paragraph.

Specification

The Examiner stated that the sequence listed on page 14 should be notated with sequence identifiers. Applicants respectfully submit that the sequence identifiers in Table 1 of page 14 were added in a response to notice to comply mailed on March 22, 2001. A copy of the March 22, 2001 response is attached hereto for the Examiner's convenience.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 48-57 and 60-62 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner stated that it is unclear what is meant by the "*" in the recited HLA-DRB1 *0401 allele, HLA-DRB1 *0404 allele, HLA-DRB1 *0405 allele, and HLA-DRB1 *0408 allele.

Applicants respectfully submit that the "*" is part of the accepted nomenclature for HLA alleles.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 48-57 and 60-62 under 35 U.S.C. § 112, first paragraph, alleging that the specification, while being enabling for the determination of developing severe disease by detecting the presence or absence of some polymorphisms in the HLA-DRB1 allele, does not reasonably provide enablement for the determination of developing severe disease by detecting the presence or absence of any polymorphism in the HLA-DRB1 allele. Specifically, the Examiner stated that it "is unclear what is meant by the '*0401'." In addition, the Examiner stated that if "the term 'HLA-DRB1 *0401' means that there is a polymorphism in the HLA-DRB1 0401 allele, then the claims are not enabled for such a broad scope."

Applicants respectfully disagree with the Examiner's conclusion that Applicants' specification does not enable claims that recite any polymorphism in an allele. Nevertheless, the present claims indicate that the HLA-DRB1 allele is an HLA-DRB1 *0401 allele, an HLA-DRB1 *0404 allele, an HLA-DRB1 *0405 allele, or an HLA-DRB1 *0408 allele. Applicants note that an HLA-DRB1 *0401 allele is a specific HLA allele. Likewise, HLA-DRB1 *0404, HLA-DRB1 *0405, and HLA-DRB1 *0408 alleles are each specific HLA alleles. Thus, the presently claimed invention is fully enabled.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 48-57 and 60-62 under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 48-57 and 60-62 under 35 U.S.C. § 103(a) as being unpatentable over Goronzy *et al.* (*J. Clin. Investigation, Inc.*, 94:2068-2076 (1994)) in view of Abril *et al.* (*Arthritis Rheum.*, 40:762 (1998)).

Applicants respectfully disagree. Claim 48 recites comparing the frequency of $CD4^{+}/CD28^{null}$ cells in the patient to a reference frequency to obtain information about the rheumatoid arthritis condition, and determining if the patient is predisposed to develop severe disease based on the information and the presence or absence of a recited HLA-DRB1 allele. The Goronzy *et al.* reference discloses that three of the five patients in the study expressed two disease-associated HLA-DRB1 alleles, one of which already developed extra-articular

manifestations. At no point does the Goronzy *et al.* reference discuss $CD4^+/CD28^{null}$ cell frequencies. The Abril *et al.* reference disclosed that a high frequency of $CD4^+$ $CD28^-$ T cells is correlated with extraarticular manifestations of rheumatoid arthritis. At no point does the Abril *et al.* reference discuss HLA-DRB1 alleles. Moreover, at no point does the combination of references teach or suggest that a person having ordinary skill in the art should assess both $CD4^+/CD28^{null}$ cell frequencies and HLA-DRB1 alleles when determining a rheumatoid arthritis patient's predisposition to develop severe disease. In fact, the combination of cited references fails to provide any indication that $CD4^+/CD28^{null}$ cell frequencies and HLA-DRB1 alleles are independent indicators that should be used together to assess a rheumatoid arthritis patient's predisposition to develop severe disease.

As stated previously, a person having ordinary skill in the art would have known from Chapman *et al.* (*J. Immunol.*, 157:4771-4780 (1996)) that $CD4^+/CD28^{null}$ cell frequencies are associated with HLA-DRB1 alleles such as an HLA-DRB1 *0401 allele. In fact, the Chapman *et al.* authors state that the "percentage of $CD28^-CD4^+$ T cells in the peripheral blood of 57 individuals was significantly correlated with specific class II MHC alleles." See, abstract. Thus, assuming one was motivated to determine a rheumatoid arthritis patient's predisposition to develop severe disease, one might have assessed either $CD4^+/CD28^{null}$ cell frequencies or HLA-DRB1 alleles, but not both. It is Applicants' specification that discloses that $CD4^+/CD28^{null}$ T cell counts are independent of HLA-DRB1 genotype. See, e.g., page 43, lines 24-25.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 48-57 and 60-62 under 35 U.S.C. §103(a).

CONCLUSION

Applicants respectfully submit that claims 48-57, and 60-62 are in condition for allowance, which action is requested. A Petition for Automatic Extension with the required fee is attached. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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